Applicants respectfully submit that, in view of the amendments to the claims, the foregoing objection to the claims has been rendered moot. Accordingly Applicants respectfully request that the Examiner reconsider and withdraw this objection.

Rejection of Claims 1-3, 11-12 and 15-16 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-3, 11-12 and 15-16 under 35 U.S.C. §112, first paragraph, because, according to the Examiner, "the specification, *while* ***being enabling for a method of identifying a compound suitable for treatment wherein the PCIP is 9q***, does not reasonably provide enablement for a method of identifying a compound suitable for treatment wherein the polypeptide is a fragment of PCIP 9q." (***Emphasis Added***). In particular, the Examiner is of the opinion that

> [c]laims 1-3, 11-12, 15-16 are overly broad in the recitation of "fragments". There is not adequate guidance as to the nature of the fragments which Applicants claim. There is insufficient guidance provided in the specification as to the relationship between the structure of PCIP 9q and its function. Without this information, it would require undue experimentation for one of skill in the art to practice a method of identifying a compound suitable for treatment wherein the polypeptide is a fragment of PCIP 9q.

Applicants respectfully submit that claims 1-3, and claims depending therefrom, have been amended such that they are no longer directed to methods which use 9q fragments. The Examiner has admitted that the instant specification is enabling for methods which use the 9q PCIP (see *supra*). Accordingly, Applicants respectfully request that the Examiner withdraw the foregoing rejection as it applies to claims 1-3, and claims depending therefrom.

Applicants respectfully traverse the foregoing rejection as it applies to newly added claims 17-19, and claims depending therefrom, for the following reasons. In contrast to the Examiner's assertions, Applicants' specification provides ample guidance regarding the structure function relationship of the 9q polypeptides and also provides

actual examples of studies performed to determine the functional significance of the various domains of the 9q polypeptides (including site directed mutagenesis and deletion analysis).

To begin with, Applicants' specification discloses at, for example, page 53, lines 11-14, as well as in Figure 21, that the 9q polypeptides of the invention contain calcium binding domains that are important for the activity of the 9q molecules.

In Example 10, Applicants also disclose the generation of N-terminal deletions of the 9q polypeptide. Applicants have demonstrated that deletion of the N-terminal residues (amino acids 2-67) of the human 9q protein did not alter the function of the 9q molecule, *e.g.*, the ability of the molecule to modulate Kv4.2 current amplitude and kinetics (page 49, line33 through page 50, line 2 of the specification). Thus, Applicants have demonstrated that the N-terminus of the 9q polypeptide is not critical for the function of this molecule.

Applicants have further demonstrated, by introducing point mutations into the EF hands of the 9q polypeptide, that these calcium binding domains are important for activity (see Example 10 at pages 49-50 of the specification).

In view of the foregoing, Applicants respectfully submit that an ordinarily skilled artisan reading Applicants' specification would have known which fragments of the 9q polypeptide can be used in the claimed methods.

Moreover, the instant specification describes extensively and in great detail how to make 9q fragments (see, for example, page 36, line 9 through page 37, line 17), how to test their functional activity (see, for example, page 10, lines 24 through page 11, line17 and Examples 7 and 8 at pages 47-48), and how to use these fragments (see, for example, page 32, line 26, through page 33, line 26).

In view of the above, Applicants respectfully submit that an ordinarily skilled artisan reading the foregoing teachings in Applicants' specification would have been able to practice the claimed invention using only routine experimentation. Accordingly, the aforementioned

rejection of the pending claims under section 112, first paragraph, is improper, and Applicants respectfuliy request that the Examiner reconsider and withdraw this rejection.

Rejection of Claims 1-3, 11-12 and 15-16 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-3, 11-12 and 15-16 under 35 U.S.C. § 112, second paragraph as "being indefinite for failing to point out and distinctly claim the subject matter which Applicant regards as the invention." In particular, the Examiner is of the opinion that

> [c]laims 1-3 are indefinite in the recitation of the term "fragment". This language is vague and indefinite since it encompasses potentially any portion of the polypeptide including a single amino acid. There is no guidance provided as to what specific sequences the term "fragment" refers to. Therefore, the metes and bounds of the claim are unclear. Claims 11-12 and 15-16 are vague and indefinite insofar as they depend on the term "fragment" in claims 1-3.

Applicants respectfully submit that claims 1-3, and claims depending therefrom, have been amended such that they no longer claim methods which use fragments of 9q. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection as it applies to claims 1-3, and claims depending therefrom.

With respect to newly added claims 17-19, and claims depending therefrom, it is Applicants' position that the terms "fragments" and "biologically active fragments" are art recognized and well accepted by those of skill in the art. Moreover, based on the ample teachings in Applicants' specification with respect to the biologically active domains of the 9q polypeptides (see above), the skilled artisan would understand what these terms mean. Accordingly, claims 17-19, and claims depending therefrom, are clear and definite, as required by 35 U.S.C. § 112, Second Paragraph and M.P.E.P. § 2171.

The Examiner has also rejected claims 1-3, 11-12 and 15-16 under 35 U.S.C. § 112, second paragraph, as being indefinite because of the recitation of the term "PCIP."

Applicants respectfully traverse the foregoing rejection on the grounds that the term PCIP is defined in Applicants' specification as referring to "[t]he nucleic acid molecules of the invention and their gene products" (*e.g.*, the nucleic acid and protein molecules having the sequences set forth as SEQ ID Nos:1- 72). Based on the foregoing teachings in Applicants' specification, the skilled artisan would understand what the term PCIP refers to.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw this section 112, Second Paragraph rejection.

Rejection of Claims 1-3, 11-12 and 15-16 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 1-3, 11-12 and 15-16 under 35 U.S.C. §102(b) as being anticipated by WO 9731112 (Li *et al.*). In particular, the Examiner is of the opinion that

> WO 9731112 discloses a method of identifying compounds that bind the NAB region of the α subunit of Shaker potassium channels (page 6, line 32 to page 7, line 9). The disorders which may be treated by the compounds identified through the use of this method include, interalia, cardiac disease, cardiac arrythrnias and cardiac dysrhythmias (page 4., line 4) Since the Shaker α subunit NAB region protein comprises "fragments" of the PCIP 9q of the present invention, the claims are anticipated.

Applicants respectfully traverse the foregoing rejection for the following reasons.

For a prior art reference to anticipate in terms of 35 U.S.C. § 102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicants respectfully submit that the NAB region of the Shaker α subunit does not comprise "fragments" nor does it comprise "biologically active fragments" of a PCIP molecule, *e.g.*, a 9q molecule. As indicated by a global alignment of the Shaker α subunit NAB region and human 9q PCIP, provided herewith as Appendix B, the Shaker α subunit is a *completely different molecule* and, contrary to the Examiners assertions, does

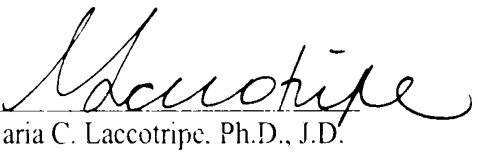
not comprise an amino acid sequence which is a fragment, *e.g.*, a biologically active fragment, of the 9q PCIP.

In view of the foregoing, Applicants' respectfully submit that PCT publication WO 9731112 fails to teach or suggest each and every element of the claimed invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing section 102(b) rejection of the pending claims.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



Maria C. Laccotripe, Ph.D., J.D.
Attorney for Applicant
Limited Recognition under 37 C.F.R. § 10.9(b)

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400
Dated: November 9, 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a 9q PCIP polypeptide ~~or a fragment thereof,~~ or a cell expressing a 9q PCIP polypeptide ~~or a fragment thereof~~, with a test compound; and

b) determining whether said 9q PCIP polypeptide ~~or fragment thereof~~, binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

2. The method of claim 1, wherein the binding of said test compound to said 9q PCIP polypeptide ~~or fragment thereof~~, is detected by a method selected from the group consisting of:

a) detection of binding by direct detection of test compound/polypeptide binding;

b) detection of binding using a competition binding assay; and

c) detection of binding using an assay for PCIP activity.

3. A method for identifying a compound suitable for treating a cardiovascular disorder, comprising:

a) incubating a cell expressing i) a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and ii) a 9q PCIP polypeptide ~~or a fragment thereof~~, in the presence and absence of a candidate compound; and

b) determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with said 9q PCIP polypeptide ~~or fragment thereof~~, thereby identifying a compound suitable for treating a cardiovascular disorder.

11. The method of any one of claims 1, 3, ~~4, 5, 6, 7, 8, 9, or 10~~, 17 or 19 wherein said cardiovascular disorder is associated with an abnormal I_{to} current.

12. The method of any one of claims 1,or 3, ~~4, 5, 6, 7, 8, 9, or 10,~~ 17 or 19wherein said PCIP is human 9q.

15. The method of any one of claims 1, 3, ~~4, 5, 6, 7, 8, 9, or 10,~~ 17 or 19, wherein said cardiovascular disorder is long-QT syndrome.

16. The method of any one of claims 1, 3, ~~4, 5, 6, 7, 8, 9, or 10,~~ 17 or 19, wherein said cardiovascular disorder is congestive heart failure.

APPENDIX A

1. A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a 9q PCIP polypeptide, or a cell expressing the 9q PCIP polypeptide with a test compound; and

b) determining whether said 9q PCIP polypeptide binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

2. The method of claim 1, wherein the binding of said test compound to said 9q PCIP polypeptide, is detected by a method selected from the group consisting of:

a) detection of binding by direct detection of test compound/polypeptide binding;

b) detection of binding using a competition binding assay; and

c) detection of binding using an assay for PCIP activity.

3. A method for identifying a compound suitable for treating a cardiovascular disorder, comprising:

a) incubating a cell expressing i) a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and ii) a 9q PCIP polypeptide, in the presence and absence of a candidate compound; and

b) determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with said 9q PCIP polypeptide, thereby identifying a compound suitable for treating a cardiovascular disorder.

11. The method of any one of claims 1, 3, 17 or 19 wherein said cardiovascular disorder is associated with an abnormal I_{to} current.

12. The method of any one of claims 1, 3, 17 or 19, wherein said 9q PCIP is human 9q.

15. The method of any one of claims 1, 3, 17 or 19, wherein said cardiovascular disorder is long-QT syndrome.

16. The method of any one of claims 1, 3, 17 or 19, wherein said cardiovascular disorder is congestive heart failure.

17. A method for identifying a compound suitable for treating a cardiovascular disorder comprising:

a) contacting a biologically active fragment of a 9q PCIP polypeptide, or a cell expressing a biologically active fragment of said 9q PCIP polypeptide with a test compound; and

b) determining whether said biologically active fragment binds to said test compound, thereby identifying a compound suitable for treating a cardiovascular disorder.

18. The method of claim 17, wherein the binding of said test compound to said biologically active fragment of a 9q PCIP polypeptide, is detected by a method selected from the group consisting of:

a) detection of binding by direct detection of test compound/biologically active fragment binding;

b) detection of binding using a competition binding assay; and

c) detection of binding using an assay for PCIP activity.

19. A method for identifying a compound suitable for treating a cardiovascular disorder, comprising:

a) incubating a cell expressing i) a potassium channel comprising a Kv4.3 or Kv4.2 subunit, or a fragment of a potassium channel comprising a Kv4.3 or Kv4.2 subunit, and ii) a biologically active fragment of a 9q PCIP polypeptide, in the presence and absence of a candidate compound; and

b) determining whether the presence of the candidate compound modulates the interaction of the potassium channel or fragment thereof with said biologically active fragment of a 9q PCIP polypeptide, thereby identifying a compound suitable for treating a cardiovascular disorder

20. The method of any one of claims 17, 18, or 19, wherein said biologically active fragment of a 9q PCIP polypeptide comprises an EF domain.

21. The method of any one of claims 17, 18 or 19, wherein said biologically active fragment of a 9q PCIP polypeptide comprises amino acid residues 68-252 of human 9q.

22. The method of any one of claims 17, 18 or 19, wherein said biologically active fragment of a 9q PCIP polypeptide comprises a calcium binding domain.

23. The method of any one of claims 17, 18 or 19, wherein said biologically active fragment of a 9q PCIP polypeptide comprises a Kv4.3 or Kv4.2 potassium channel α subunit binding domain.

Appendix B

lalign output for Human 9q vs. NAB region

[ISREC-Server] Date: Thu Nov 8 23:06:11 MET 2001

LALIGN finds the best local alignments between two sequences version 2.0u66 September 1998
Please cite: X. Huang and W. Miller (1991) Adv. Appl. Math. 12:373-381

```
 Comparison of:
(A) /tmp/www-sib/lalign.5839.1.seq Human 9q
(B) /tmp/www-sib/lalign.5839.2.seq NAB region
 using matrix file: BL50, gap penalties: -14/-4

 75.9% identity in 54 aa overlap; score:   49 E(10,000): 5.3e+02

         70        80        90        100       110       120
Human  RPRLLDPDSVDDEPELSTVCHRPEGLEQLQE-QTKPTRKELQVLYRGPKNECPS
       ::  :  : .   :. .  :  ::: :. .   ..: .... .: . :..  :.
NAB    RPYQLG-DEALAAPREDEGCL-PEGGEDEKPLPSQPPQRQVWLLPEYPESSGPA
              90        100       110       120       130

 29.7% identity in 37 aa overlap; score:   45 E(10,000): 1.2e+03

         10        20        30        40
Human  ESLSDSRDLDGSYDQLTGHPPGPTKKALKQRPLKLLP
       :.:.  :. .:    .  :.   :  .   :: . :::
NAB    EALAAPREDEGCLPE-GGEDEKPLPSQPPQRQVWLLP
      90        100       110       120

 54.5% identity in 11 aa overlap; score:   43 E(10,000): 1.7e+03

         130
Human  ENPKQIYSQPP
       :. : . ::::
NAB    EDEKPLPSQPP
        110
```

Back to ISREC bioinformatics group home page